Antiretroviral Therapy for HIV Infection

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Overview

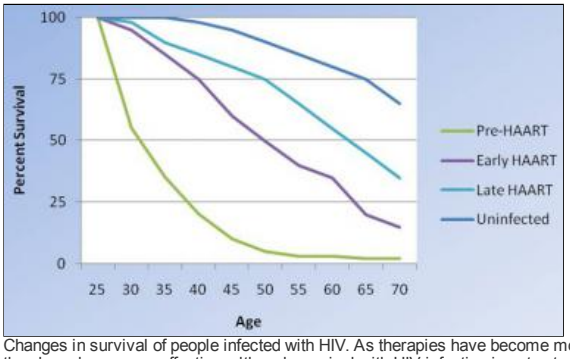
Background

An estimated 33 million people are infected with HIV worldwide.[1] In the United States, more than 1.2 million people have HIV infection, and almost 1 in 7 (14%) are unaware of their infection. The estimated incidence of HIV in the United States has remained stable in recent years, at about 50,000 new infections occurring each year.[2]

Significant advances in antiretroviral therapy have been made since the introduction of zidovudine (AZT) in 1987.

With the advent of highly active antiretroviral therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression.[3]

Excess mortality among patients with AIDS was nearly halved in the HAART era (see the image below), but it remains approximately 5 times higher in patients with AIDS than in HIV-infected patients without AIDS. The strongest risk factors for excess mortality were viral load greater than 400 copies/mL (compared with < 400 copies/mL), $CD4^+$ count less than 200 cells/mL (compared with >200 cells/mL), and cytomegalovirus retinitis.[4]



Changes in survival of people infected with HIV. As therapies have become more aggressive, they have been more effective, although survival with HIV infection is not yet equivalent to that in uninfected people. Modified from an original published by Lohse et al (2007), "Survival of persons with and without HIV infection in Denmark, 1995-2005."

The CD4+ cell count thresholds for HAART initiation were recently raised from 350 to 500 cells/mL in the United States and from 200 to 350 cells/mL in mid- and low-income countries. Data suggest that these recommendations mean a substantial increase in the number of patients who will require treatment and need early HIV testing.[5]

HAART provides effective treatment options for treatment-naive and treatment-experienced patients. Six classes of antiretroviral agents currently exist, as follows:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Integrase inhibitors (INSTIs)
- Fusion inhibitors (FIs)
- Chemokine receptor antagonists (CCR5 antagonists)

Each class targets a different step in the viral life cycle as the virus infects a $CD4^+$ T lymphocyte or other target cell. The use of these agents in clinical practice is largely dictated by their ease or complexity of use, side-effect profile, efficacy based on clinical evidence, practice guidelines, and clinician preference.

Resistance, adverse effects, pregnancy, and coinfection with hepatitis B virus, or hepatitis C virus present important challenges to clinicians when selecting and maintaining therapy.

This article reviews the mechanism of action, resistance, pharmacokinetics, and adverse effects of each of these classes, as well as current treatment guidelines for their use in adults and adolescents with HIV infection. Also discussed are the important challenges involved in selecting and maintaining antiretroviral therapy for pregnant women and patients with acute HIV infection, hepatitis B or C coinfection, or *Mycobacterium tuberculosis* coinfection.

For additional information on HIV disease, see the Medscape Reference articles HIV Disease and Pediatric HIV.

Table of FDA-Approved Antivirals and Regimens

Individual antiretroviral drugs are described in Table 1, below.

Table 1. Classification and Summary of US FDA–Approved Antiretroviral Agents[6]
(Open Table in a new window)

Name	Dosage Form(s)	Adult Dose	Adverse Events
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Abacavir (Ziagen)	300-mg tablet; 20-mg/mL oral solution	600 mg PO qd or 300 mg PO bid	Hypersensitivity reaction (may include fever, rash, nausea, vomiting, diarrhea, malaise, shortness of breath, cough, pharyngitis); patients positive for HLA-B*5701 are at highest risk for hypersensitivity (perform HLA screening before initiating)
Didanosine (Videx, Videx EC)	125-mg, 200-mg, 250-mg, 400-mg enteric-coated capsule; 10-mg/mL suspension	>60 kg: 400 mg PO qd < 60 kg: 250 mg PO qd Take 30 min ac or 2 hr pc Oral solution: Divide daily dose bid	Peripheral neuropathy, pancreatitis, nausea, lactic acidosis
Emtricitabine (Emtriva)	200-mg capsule; 10-mg/mL oral solution	200 mg PO qd or 240 mg (24 mL) oral solution PO qd	Minimal toxicity, hyperpigmentation
Lamivudine (Epivir)	150-mg, 300-mg tablet; 10-mg/mL oral solution	300 mg PO qd or 150 mg PO bid	Minimal toxicity, severe acute exacerbation of hepatitis may occur with HBV-coinfection upon discontinuation
Stavudine (Zerit)	15-mg, 20-mg, 30-mg, 40-mg capsule; 1-mg/mL oral solution	>60 kg: 40 mg PO bid < 60 kg: 30 mg PO bid	Peripheral neuropathy, pancreatitis, lactic acidosis, lipoatrophy, hyperlipidemia
Tenofovir (Viread)	300-mg tablet	300 mg PO qd	Nausea, vomiting, diarrhea, headache, asthenia, renal insufficiency[7]
Zalcitabine (Hivid) *Product discontinued*	0.375-mg, 0.75-mg tablet	0.75 mg PO tid	Peripheral neuropathy, pancreatitis, lactic acidosis, stomatitis
	300-mg tablet; 100-mg capsule;		

Zidovudine (Retrovir)	10-mg/mL oral solution; 10-mg/mL intravenous solution	300 mg PO bid or 200 mg PO tid	Nausea, vomiting, headache, asthenia, anemia, neutropenia
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Delavirdine (Rescriptor)	100-mg, 200-mg tablets	400 mg PO tid	Rash, headache
Efavirenz (Sustiva)	600-mg tablet; 50-mg, 200-mg capsule	600 mg PO qd Take on empty stomach to decrease adverse effects	Rash, CNS (eg, somnolence, vivid dreams, confusion, visual hallucinations), hyperlipidemia
Etravirine (Intelence)[d]	100-mg, 200-mg tablets	200 mg PO bid	Rash, nausea
Nevirapine (Viramune, Viramune XR)	200-mg tablet; 400 mg XR tablet; 10-mg/mL suspension	200 mg PO bid[a] XR: 400 mg PO qd	Rash, hepatitis
Rilpivirine (Edurant)	25-mg tablet	25 mg PO qd with a meal	Depressive disorders, insomnia, headache, rash
Protease inhibitors (PIs)			
Atazanavir (Reyataz)	100-mg, 150-mg, 200-mg, 300-mg capsules	400 mg PO qd or 300 mg + ritonavir 100 mg PO qd	Indirect hyperbilirubinemia, prolonged PR interval, hyperglycemia, skin rash (20%), hyperlipidemia
Darunavir (Prezista)	75-mg, 150-mg, 300-mg, 400-mg, 600-mg tablets	800 mg qd + ritonavir 100 mg PO qd[b] or 600 mg bid + ritonavir 100 mg PO bid	Rash, nausea, diarrhea, hyperlipidemia, hyperglycemia
Fosamprenavir (Lexiva)	700-mg tablet; 50-mg/mL oral suspension	700 mg bid + ritonavir 100 mg PO bid or 1400 mg PO bid or 1400 mg + ritonavir 100-200 mg PO qd[b] Suspension: Take without food Boosted with RTV: Take with food	Rash, nausea, vomiting, diarrhea, hyperlipidemia, hyperglycemia
		800 mg PO q8h	

Indinavir (Crixivan)	100-mg, 200-mg, 400-mg capsules	800 mg PO bid + ritonavir 100-200 mg PO bid Take 1 h ac or 2 h pc; may take with skim milk or low-fat meal	Nephrolithiasis, nausea, indirect hyperbilirubinemia, hyperlipidemia, hyperglycemia
Lopinavir/ritonavir (Kaletra)	100-mg/25-mg, 200-mg/50-mg tablets; 80-mg/20-mg per mL oral solution	400 mg/100 mg PO bid or 800 mg/200 mg PO qd[b] Oral solution: Take with meals	Nausea, vomiting, diarrhea, asthenia, hyperlipidemia, hyperglycemia
Nelfinavir (Viracept)	250-mg, 625-mg tablets, 50 mg/g oral powder	1250 mg PO bid or 750 mg PO tid (Nelfinavir cannot be boosted) Take with food	Diarrhea, hyperlipidemia, hyperglycemia
Ritonavir (Norvir)	100-mg tablet; 100-mg soft gelatin capsule; 80-mg/mL oral solution	Boosting dose for other protease inhibitors: 100-400 mg/d (refer to other protease inhibitors for specific dose) Nonboosting dose (Ritonavir used as sole protease inhibitor): 600 mg bid[c]	Nausea, vomiting, diarrhea, asthenia, hyperlipidemia, oral paresthesias, hyperglycemia
Saquinavir (Invirase)	500-mg tablet; 200-mg hard gelatin capsule	1000 mg + ritonavir 100 mg PO bid Unboosted saquinavir is not recommended Take with food, or within 2 h pc	Nausea, diarrhea, headache, hyperlipidemia, hyperglycemia, PR and QT interval prolongation
Tipranavir (Aptivus)[d]	250-mg soft gelatin capsule 100-mg/mL oral solution	500 mg + ritonavir 200 mg PO bid Unboosted tipranavir is not recommended	Hepatotoxicity, rash, hyperlipidemia, hyperglycemia, intracranial hemorrhage (rare cases reported)
Integrase inhibitors (II)			
		400 mg PO bid	Nausea, diarrhea,

Raltegravir (Isentress)	400-mg tablet	With rifampin: 800 mg PO bid	headache, CK elevations, myopathy/rhabdomyolysis (rare)
Dolutegravir (Tivicay)	50-mg tablet	50 mg PO once daily With UGT1A/CY3A inducers (eg, efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, rifampin): 50 mg PO BID	Cholesterol and TG elevations, CK elevations, liver enzyme elevations, hyperglycemia
Elvitegravir (Vitekta)[f]	85-mg, 150-mg tablet	85 mg PO once daily plus atazanavir or lopinavir plus ritonavir or 150 mg PO once daily plus darunavir or fosamprenavir or tipranavir plus ritonavir	Immune reconstitution syndrome
Chemokine receptor antagonist (CCR5 antagonist)			
Maraviroc (Selzentry)	150-mg, 300-mg tablets	300 mg PO bid 150 mg PO bid (CYP3A4 inhibitors ± inducers) 600 mg PO bid (CYP3A4 inducers)	Constipation, dizziness, infection, rash
Fusion inhibitor (FI)			
Enfuvirtide (Fuzeon)[d]	90-mg/mL powder for injection	90 mg SC bid	Injection-site reactions (eg, pain, erythema, induration, nodules)
Combination formulations			
Stribild – elvitegravir (150 mg) + cobicistat[e] (150 mg) + emtricitabine (200 mg) + tenofovir DF (300 mg) qd; this is a complete once-daily regimen			
Genvoya – elvitegravir (150 mg) + cobicistat (150 mg) + emtricitabine (200 mg) + tenofovir AF[g] (10 mg) qd; this is a complete once-daily regimen			
Odefsey – emtricitabine (200 mg) + rilpivirine (25 mg) + tenofovir AF (25 mg) qd; this is a complete once-daily regimen			
Descovy – emtricitabine (200 mg) + tenofovir AF (25 mg) qd			
Epzicom - Abacavir (600 mg) + lamivudine (300 mg) qd			
Triumeq – Abacavir (300 mg) + dolutegravir (50 mg) + lamivudine (300 mg) qd			
Trizivir - Abacavir (300 mg) + lamivudine (150 mg) + zidovudine (300 mg) bid			
Truvada - Tenofovir DF (300 mg) + emtricitabine (200 mg) qd			

Atripla - Tenofovir DF (300 mg) + emtricitabine (200 mg) + efavirenz (600 mg) qd

Complera – Tenofovir DF (300 mg) + emtricitabine (200 mg) + rilpivirine (25 mg) qd

Combivir - Zidovudine (300 mg) + lamivudine (150 mg) bid

Evotaz – Atazanavir (300 mg) + cobicistat (150 mg) qd

Prezcobix – Darunavir ethanolate (800 mg) + cobicistat (150 mg) qd

*Dosing guides assume an absence of drug-drug interactions (except ritonavir) and normal renal and hepatic function.

[a] Administer 200 mg qd for 2 weeks, then increase to 200 mg bid.

[b] Approved only for antiretroviral treatment–naïve patients (or with darunavir, treatment-experienced patients without darunavir-resistant mutations).

[c] Titrate dose over 14 days, beginning with 300 mg bid on days 1-2, 400 mg bid on days 3-5, and 500 mg bid on days 6-13.

[d] Approved only for antiretroviral treatment–experienced patients with drug resistance.

[e] CYP3A4 inhibitor; enhances the systemic exposure of CYP3A substrates, such as elvitegravir, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

[f] See prescribing information for more details

[g] E/C/F/tenofovir alafenamide (TAF)

Nucleoside Reverse Transcriptase Inhibitors

The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) were the first agents available for the treatment of HIV Infection. Although less potent against HIV than non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand-transfer inhibitors (INSTIs), the NRTIs have had a central role in antiretroviral treatment and remain part of the current standard of care.[8, 6] They exhibit activity against HIV-1 and HIV-2.[9]

A total of 9 drugs make up the NRTI class; 8 are currently commercially available in the United States, as follows:

- Abacavir (ABC, Ziagen)
- Didanosine (ddI, Videx)
- Emtricitabine (FTC, Emtriva)
- Lamivudine (3TC, Epivir)
- Stavudine (d4T, Zerit)
- Tenofovir DF (TDF, Viread, part of the combination product Stribild)
- Tenofovir AF (TAF, part of the combination product Genvoya)
- Zalcitabine (ddC, Hivid; no longer available in the United States)
- Zidovudine (ZDV, Retrovir; formerly azidothymidine [AZT])

Mechanism of action

NRTIs interrupt the HIV replication cycle via competitive inhibition of HIV reverse transcriptase and termination of the DNA chain.[10] Reverse transcriptase is an HIV-specific DNA polymerase that allows HIV RNA to be transcribed into single-strand and ultimately double-strand proviral DNA and incorporated into the host-cell genome. Proviral DNA chain elongation is necessary before genome incorporation can occur and is accomplished by the addition of purine and pyrimidine nucleosides to the 3’ end of the growing chain.

NRTIs are structurally similar to the DNA nucleoside bases and become incorporated into the proviral DNA chain, resulting in termination of proviral DNA formation.[11] Tenofovir, lamivudine, and emtricitabine exhibit activity against hepatitis B virus (HBV) in addition to HIV and are frequently incorporated into antiretroviral regimens for patients with HIV and HBV coinfection.[6]

Resistance

Resistance to NRTIs occurs by one of two mechanisms: (1) impaired incorporation into the proviral DNA chain or (2) removal from the proviral DNA chain.[12] Mutations typically occur gradually, with accumulation of several mutations required before clinically significantly resistance develops. An exception is the M184V mutation, which confers high-level resistance to lamivudine and emtricitabine in a single step. Mutations that selectively impair incorporation into the proviral DNA chain include M184V, Q151M, and K65R.

Thymidine analog mutations (mutations associated with zidovudine resistance [M41L, D67N, K70R, L210W, T215Y, T215F, K219Q, K219E]) remove NRTIs from the DNA chain by fostering a conformational change in the reverse transcriptase domain that allows the addition of ATP or pyrophosphate to the end. This placement causes a break in the proviral DNA and NRTI bond, enabling continued elongation of the proviral DNA strand.[11, 12]

Pharmacokinetics

NRTIs are prodrugs and must undergo phosphorylation by intracellular kinases to exert their activity. Collectively, the oral bioavailability of NRTIs ranges from 25%-93%, with tenofovir and didanosine on the lower end of the spectrum. Food does not significantly affect absorption of any of the NRTIs except didanosine, which must be taken on an empty stomach to achieve optimal absorption and drug levels.

Although serum half-lives of NRTIs are relatively short, intracellular drug levels are the best indicator for drug activity and determine the dose administered for each NRTI.[13] Most NRTIs are renally eliminated and require dose adjustments in patients with renal insufficiency; the exception is abacavir, which is given at the normal dose regardless of creatinine clearance.

NRTIs are not metabolized by the cytochrome P450 system; therefore, minimal drug-drug interactions occur. Interactions that have been found to be clinically significant involve didanosine. When given in combination with tenofovir, didanosine levels are higher than expected, and lower doses must be given to avoid potentially serious adverse effects. A similar scenario has been demonstrated when didanosine is combined with ribavirin in the treatment of patients with HIV and hepatitis C virus (HCV) coinfection. This combination should be avoided.[6]

Tenofovir alafenamide (TAF) is a prodrug of tenofovir that has high antiviral efficacy similar at a dose less than one-tenth that of the original formulation of tenofovir prodrug (ie, tenofovir disoproxil fumarate [TDF]). TAF provides lower blood levels, but higher intracellular levels compared with TDF.[14, 15]

Adverse events

Adverse effects of the NRTI class include mitochondrial toxicities (eg, lactic acidosis, pancreatitis, peripheral neuropathy, hepatic steatosis, lipoatrophy).[6] Mitochondrial toxicities are due to NRTI binding to human mitochondrial DNA polymerase-γ enzyme, impairing cellular respiration. Under these conditions, normal aerobic metabolism shifts to an anaerobic process, resulting in the above manifestations.

Antiretroviral therapy reduces the risk of chronic kidney disease along with CD4 cell restoration and suppression of plasma viral load, despite an increased risk that is associated with initial treatment regimens that include tenofovir plus a ritonavir-boosted protease inhibitor.[16]

Binding affinity for mitochondrial DNA polymerase-γ by each NRTI is predictive of adverse-effect potential and varies as follows (in decreasing order of affinity): zalcitabine, didanosine, stavudine, lamivudine/emtricitabine, zidovudine, abacavir, and tenofovir.[17, 18]

Individual drug-specific adverse effects include bone marrow suppression, myopathy, and headache with zidovudine and a systemic hypersensitivity reaction with abacavir.[6] Abacavir and didanosine have been associated with an increased risk for adverse cardiovascular events.[19]

Initiation of ART is associated with increased bone turnover and bone loss from the spine and hip, with a number of subjects losing about 6% bone mass density within 1 year after starting treatment.[20] Adverse effects with the remaining NRTIs are included in Table 1.[6]

Although not recommended for patients with severe renal impairment, those with moderate renal impairment can take TAF. Tenofovir AF appears to be associated with less kidney toxicity and less decreases in bone density than previously approved tenofovir-containing regimens.[14, 21] Patients given E/C/F/tenofovir alafenamide had significantly smaller mean serum creatinine increases than those given E/C/F/tenofovir disoproxil fumarate (0.08 vs 0.12 mg/dL; P<0.0001), significantly less proteinuria (median % change -3 vs 20; P<0.0001), and a significantly smaller decrease in bone mineral density at spine (mean % change -1·30 vs -2·86; P<0·0001) and hip (-.0·66 vs -2·95; P<0.0001) at 48 weeks.[14]

In clinical trials, patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir AF (Genvoya) showed greater increases in serum lipids (total cholesterol and low-density lipoprotein) than those receiving other ART regimens, but the total cholesterol/high-density lipoprotein ratio was unchanged for both.[14]

Non-nucleoside Reverse Transcriptase Inhibitors

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) were introduced in 1996 with the approval of nevirapine. NNRTIs exhibit potent activity against HIV-1 and are part of preferred initial regimens.[8, 6] Efavirenz, in particular, confers the most significant inhibition of viral infectivity among the NNRTIs.[8]

First-generation NNRTIs include delavirdine (Rescriptor), efavirenz (Sustiva), and nevirapine (Viramune). Second-generation NNRTIs currently include etravirine (Intelence), approved for use in the United States in 2008, and rilpivirine (Edurant) [22] approved in 2011.

All NNRTIs exhibit the same mechanism of action. First-generation NNRTIs share similar resistance patterns, whereas etravirine and rilpivirine display a more unique resistance profile.[23] Their pharmacokinetic properties and adverse-effect profiles have important differences.

Mechanism of action

HIV reverse transcriptase is a heterodimer composed of 2 subunits (p66 and p51). [24] NNRTIs bind the p66 subunit at a hydrophobic pocket distant from the active site of the enzyme. This noncompetitive binding induces a conformational change in the enzyme that alters the active site and limits its activity.[24]

Etravirine differs from first-generation NNRTIs in its ability to bind at this site despite the presence of some mutations that limit the efficacy of first-generation agents. It is a highly flexible molecule that is able to rotate within the binding site to allow multiple binding conformations.[25]

All four NNRTIs exhibit activity against HIV-1 isolates. In vitro studies have shown that etravirine also has activity against HIV-2.[26]

Resistance

Mutations within the reverse transcriptase gene domain alter the ability of the NNRTIs to bind the enzyme. First-generation NNRTIs have a low genetic barrier to resistance, whereby a single mutation in the binding site can decrease the ability of the drug to bind, significantly diminishing activity.[27] First-generation NNRTI resistance has been associated with mutations at multiple codons; however, the presence of either a K103N or Y181C mutation is sufficient to cause clinical failure of delavirdine, efavirenz, and nevirapine.[27]

Associated mutations include the following[27] :

- Delavirdine - A98G, L100I, K101E, K103N, K103T, V179D, Y181C, Y188L, M230L, P236L, Y318F
- Efavirenz - L100I, K101E, K103N, V108I, V179D, Y181C, Y188L, G190S, M230L
- Nevirapine - A98G, L100I, K101E, K103N, V106A, V106I, V108I, Y181C, Y191I, Y188C, Y188H, G190A, P225H, M230L, P236L, Y318W

Etravirine has a higher genetic barrier to resistance than other currently available NNRTIs. A single mutation at 103 or 181 is insufficient to cause clinical failure of etravirine.[28] Clinical trials have identified 17 resistance mutations associated with decreased response to etravirine: V90I, A98G, L100I, K101E, K101H, K101P, V106I, E138A, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, G190S, and M230L.[29]

A 2008 study found that different mutations affect viral susceptibility to etravirine to varying degrees. Each etravirine resistance-associated mutation was assigned a relative weight. The virologic response was found to be a function of the number and weight of resistance mutations. With a cumulative score of 0-2, a response rate of 74% was reported. With a score of 2.5-3.5 or 4 or more, response rates of 52% and 38%, respectively, were reported.[29]

The etravirine mutation weighting scheme is as follows[29] :

- 3 - Y181I, Y181V
- 2.5 - L100I, K101P, Y181C, M230L
- 1.5 - V106I, E138A, V179F, G190S
- 1 - V90I, A98G, K101E, K101H, V179D, V179T, G190A

Pharmacokinetics

NNRTIs display considerable interindividual variability in their pharmacokinetic properties. All currently approved NNRTIs utilize the cytochrome P450 system for metabolism and exert varying induction and inhibition effects on specific isoenzymes (eg, CYP3A4, CYP2C9). This results in a significant potential for drug-drug interactions (see Table 2 and Table 3, under Tables of Antiretroviral Drug Interactions, below).[25, 30]

Delavirdine primarily uses the 3A4 isoenzyme for metabolism. Nevirapine is metabolized mainly by 3A4 with some secondary metabolism through 2B6. Efavirenz is primarily metabolized through 2B6 and secondarily through 3A4. Etravirine is a substrate of 3A4, 2C9, and 2C19.

With the exception of nevirapine, the NNRTIs are highly protein-bound (98-99%), primarily to albumin and alpha$_1$ acid glycoprotein. The serum half-lives of the NNRTIs are fairly extended, ranging from 25-55 hours, except for delavirdine, which has a shorter half-life (2-11 h).[25, 30]

Adverse events

Rash, which is the most common adverse effect associated with all NNRTIs,[6] usually develops within the first few weeks of therapy and resolves with continued treatment.[6, 25, 31] All NNRTIs except etravirine have the ability to cause some degree of hepatotoxicity.[25, 32] Delavirdine and efavirenz can increase transaminase levels, while nevirapine can cause severe toxicity, including hepatic necrosis in patients with CD4 counts that exceed 250 cells/µL.[6, 33]

Efavirenz is unique among NNRTIs, causing CNS effects such as insomnia, vivid dreaming, dizziness, confusion, and hallucinations.

Tolerance to efavirenz-related CNS adverse effects commonly occurs after several weeks of therapy. Bedtime administration and avoidance of food at the time of administration can minimize the intensity of adverse effects. CNS effects may persist in a small number of patients, requiring drug discontinuation.[6]

Gutiérrez-Valencia et al found that gradual upward titration of efavirenz over 2 weeks reduced neuropsychiatric symptoms and insomnia. In a randomized, double-blind, controlled trial that included 114 patients, those patients who received a full dose of 600 mg daily from day 1 had a higher incidence and severity of dizziness (66% vs 32.8%), hangover (45.8% vs 20.7%), impaired concentration (22.9% vs 8.9%), and hallucinations (6.1% vs 0%) during the first week, compared with patients who had gradual efavirenz titration to 600 mg daily by day 14.[34]

During week 2, the incidence of these aforementioned adverse events was similar in each group; however, severity was greater in the full-dose group. Virologic and immunologic efficacy was similar in both groups.[34]

Protease Inhibitors

HIV protease inhibitors (PIs) were first introduced in 1995 and are an integral part of treatment of HIV infection.[6] A total of 8 compounds are approved for use, as follows:

- Atazanavir (Reyataz)
- Darunavir (Prezista)
- Fosamprenavir (Lexiva)
- Indinavir (Crixivan)
- Lopinavir/ritonavir (Kaletra)
- Nelfinavir (Viracept)
- Saquinavir (Invirase)
- Tipranavir (Aptivus)

Although all protease inhibitors exhibit the same mechanism of action, they have important differences in pharmacokinetics, efficacy, and adverse event profiles.

Mechanism of action

HIV protease is a 99-amino-acid, aspartic acid protein and is responsible for maturation of virus particles late in the viral life cycle. HIV protease systematically cleaves individual proteins from the *gag* and *gag -pol* polypeptide precursors into functional subunits for viral capsid formation during or shortly after viral budding from an infected cell.

HIV protease inhibitors function as competitive inhibitors that directly bind to HIV protease and prevent subsequent cleavage of polypeptides.[35] They exhibit activity against clinical isolates of both HIV-1 and HIV-2.[35]

Resistance

Resistance to HIV protease results from mutations both inside and outside the active protease domain.[36] Resistance typically occurs through the development of one or more major mutations, which produce conformational changes in the protease binding site, followed by secondary compensatory mutations that improve enzymatic activity and, in some cases, viral fitness.[36]

Resistance to first-generation protease inhibitors (indinavir, ritonavir, nelfinavir, saquinavir) occurs with the development of one or more of the following primary mutations[36] :

- G48V, L90M (saquinavir)
- M46I, V82A/L/F, I84V (indinavir)
- V82A/L/F, I84V (ritonavir)
- D30N, L90M (nelfinavir)
- I50L, I84V, N88S (atazanavir)
- I50V, I84V (fosamprenavir)

Multiple mutations are typically necessary to cause high-level resistance to ritonavir-boosted (ie, coadministered with low-dose ritonavir to decrease intestinal and hepatic 3A metabolism, thereby increasing protease inhibitor serum concentration levels) protease inhibitors, which exhibit a higher genetic threshold for resistance than unboosted (ie, not coadministered with low-dose ritonavir) protease inhibitors.[37] Cross-resistance to other protease inhibitors develops as the number of mutations increases.

The second-generation protease inhibitors lopinavir/ritonavir, darunavir, and tipranavir may retain activity in the presence of resistance to first-generation agents. Lopinavir/ritonavir requires the accumulation of 7 or more mutations before high-level resistance develops.[36] Darunavir and tipranavir typically retain activity against lopinavir/ritonavir and first-generation protease inhibitor–resistant strains.[36]

Eleven resistance mutations have been described for darunavir; accumulation of 3 or more is associated with virologic failure. Tipranavir also requires accumulation of multiple nonoverlapping mutations before high-level resistance develops.[36]

A review of 2725 HIV isolates for protease inhibitor susceptibility revealed that certain mutations could result in increased susceptibility to a particular drug, and that some effects on resistance had been underestimated.[38] The study concluded that cross-resistance between the various protease inhibitors now and in the future may be missed without systematic analysis of the effects of specific mutations.

Pharmacokinetics

Protease inhibitors exhibit substantial interpatient and intrapatient variability in pharmacokinetics.[39] Significant first-pass metabolism by cytochrome P450 (CYP) 3A4 and 3A5 and intestinal efflux by p-glycoprotein is observed.[39] With the exception of indinavir, protease inhibitors are highly protein-bound (97-99%), primarily to albumin and alpha$_1$ acid glycoprotein.[6] Distribution into the CNS is limited. Protease inhibitors have relatively short serum half-lives, ranging from 1.5-2 hours for indinavir and 7 hours for atazanavir.[6]

Reliance on metabolism through CYP3A4 results in significant potential for drug-drug interactions with other medications cleared through this pathway (see Table 2 and Table 3). Interactions with medications cleared through other CYP450 isoenzymes and phase II pathways (eg, glucuronidation) are possible, depending on the individual protease inhibitor.[6]

Low-dose ritonavir (100-200 mg) is frequently coadministered with other protease inhibitors to block intestinal and hepatic 3A metabolism. The addition of low-dose ritonavir improves pharmacokinetic variability, resulting in more consistent serum concentrations throughout the dosing interval and improved treatment response.[39] Cobicistat is a newer agent that also blocks 3A metabolism and is used to enhance the pharmacokinetic profile of protease inhibitors.

Adverse events

Common adverse events associated with protease inhibitors include gastrointestinal side effects (diarrhea, nausea, vomiting) and metabolic complications (dyslipidemia, insulin resistance, lipodystrophy).

Metabolic complications are common in patients receiving protease inhibitor therapy and represent an important consideration in selecting antiretroviral therapy. Dyslipidemia develops in up to 70% of patients receiving protease inhibitors and commonly requires institution of lipid-lowering therapy (ie, statins, fibrates, omega3 fatty acids).

Drug interactions can preclude the use of some lipid-lowering agents (see Table 2). Lifestyle and genetic predisposition are important contributing factors to the type and severity of lipid abnormalities.[40]

In 1997, the FDA required that all protease inhibitors include labeling regarding the potential for hyperglycemia and diabetes mellitus with therapy; however, the different protease inhibitors have significantly different propensities for affecting glucose metabolism. Indinavir exhibits the greatest potential for altering glucose metabolism.

Modest effects have been observed with nelfinavir, lopinavir/ritonavir, fosamprenavir, and tipranavir. Atazanavir (boosted or unboosted), darunavir, and saquinavir appear to have limited effect on insulin sensitivity and glucose homeostasis.[41]

Altered fat distribution (fat redistribution) occurs in 40-50% of patients receiving protease inhibitors in combination with nucleoside reverse transcriptase inhibitors (NRTIs).[42] Common manifestations include fat accumulation (increased anterior cervical and dorsocervical fat, increased breast fat, centripetal obesity) or fat loss (sunken cheeks, wasted buttocks and extremities). Although both abnormalities may develop in the same patient, they are considered independent entities.

Fat accumulation has been primarily associated with protease inhibitor therapy; however, more recent data demonstrate that it occurs with both protease inhibitor–and nonnucleoside reverse transcriptase inhibitors (NNRTI)–based regimens.

Numerous management strategies have been explored (eg, metformin, recombinant human growth hormone, diet and exercise), with mixed results. Conversion from protease inhibitor–based therapy to a protease inhibitor–sparing regimen does not result in significant improvement and is not recommended.[43]

Adverse effects that occur with individual protease inhibitors need to be considered when selecting therapy for patients with other comorbidities.

Asymptomatic hyperbilirubinemia is common in patients who receive atazanavir and indinavir but does not require discontinuation of therapy in the absence of concomitant elevation in levels of liver transaminases.[6] Nephrolithiasis occurs with indinavir and, less commonly, atazanavir.[6]

Cardiac conduction abnormalities (atrioventricular block, bundle branch block) develop in 5% of patients receiving atazanavir and have been reported with other protease inhibitors (ritonavir, lopinavir/ritonavir, nelfinavir).[44]

Tipranavir may elevate levels of liver transaminases and should be avoided in patients with hepatitis B or hepatitis C coinfection. Intracranial bleeding events have been reported during tipranavir therapy.[6]

Integrase Strand-Transfer Inhibitors

The crystal structure of HIV integrase was first described in 1994 and led to the identification of novel inhibitors.[45] No homolog for HIV integrase exists in humans; therefore, identification of selective inhibitors is expected to result in a low frequency of adverse effects.[46, 47] The FDA approved raltegravir (Isentress) in 2007 as the first integrase strand-transfer inhibitor (INSTI) available for use.[48]

Elvitegravir (Vitekta) is another agent integrase inhibitor that is used in combination with an HIV protease inhibitor (ie, atazanavir, lopinavir, darunavir, fosamprenavir, or tipranavir) and coadministered with ritonavir plus other antiretroviral drug(s) as indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

Elvitegravir was initially approved as a component of the FDA-approved 'quad' pill, elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild). The 4-component tablet contains a complete once-daily regimen for treatment-naïve adults and includes elvitegravir, cobicistat (a CYP3A4 inhibitor without antiviral activity), emtricitabine, and tenofovir.[49] Approval of the ART fixed-dose combination product was based on analyses of 48-week data from 2 randomized, double-blind, active-controlled trials in treatment-naïve, HIV-1 infected individuals (n=1408). Results showed a single tablet regimen of Stribild met its primary objective of noninferiority compared to (efavirenz/emtricitabine/tenofovir) fixed-dose combination (Atripla) and to a regimen containing ritonavir-boosted atazanavir plus emtricitabine/tenofovir (Truvada).[50, 51]

Dolutegravir (Tivicay) was approved by the FDA in August 2013. An integrase strand transfer inhibitor (INSTI), dolutegravir was approved by the FDA for treatment of HIV-1 infection in combination with other antiretroviral agents in adults and children aged 12 years or older who weigh at least 40 kg.

A wide-ranging phase III trial program included 2 trials in treatment-naïve patients. The first trial included 822 HIV-infected, treatment-naïve patients randomized to receive either dolutegravir (50 mg once daily) or raltegravir (400 mg twice daily) in combination with a fixed-dose dual-NRTI treatment. At week 48, virologic suppression was similar between the 2 groups; 88% for dolutegravir and 86% for raltegravir.[52]

The second trial also included treatment-naïve patients (n=833) and compared a once-daily dolutegravir regimen plus abacavir/lamivudine to once-daily efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla). A statistically significant improvement in virologic suppression was observed with dolutegravir (88%) compared with Atripla (81%).[53]

A third phase III trial studied 719 treatment-experienced patients who were failing on current therapy, but who had not previously been treated with an integrase inhibitor. Participants were randomized to once-daily dolutegravir 50 mg or twice-daily raltegravir 400 mg. At week 24, 79% of patients on the regimen containing dolutegravir were virologically suppressed compared with 70% of patients on the regimen containing raltegravir.[54]

The VIKING-3 trial studied 183 treatment-experienced patients with resistance to multiple classes of HIV medicines, including resistance to integrase inhibitors. Researchers evaluated the effectiveness of twice-daily dolutegravir on viral load in these patients and found the regimen improved virologic suppression at 24 weeks (63%). However, poor response was observed with INSTI-resistance involving Q148 plus 2 or more INSTI resistance substitutions.[55]

Approval of dolutegravir for the indication in children aged 12 years or older was based on data in integrase-naïve patients.

Mechanism of action

HIV integrase is responsible for the transport and attachment of proviral DNA to host-cell chromosomes, allowing transcription of viral proteins and subsequent assembly of virus particles.[56] Proviral integration involves 2 catalytic reactions, as follows:

- 3'-processing in the host-cell cytoplasm to prepare proviral strands for attachment
- Strand transfer whereby proviral DNA is covalently linked to cellular DNA

These agents competitively inhibit the strand transfer reaction by binding metallic ions in the active site.[57, 58]

Resistance

Mutations in the integrase gene are associated with resistance to raltegravir and elvitegravir.[59, 60, 61] Two primary resistance pathways associated with raltegravir treatment failures in the BENCHMRK-1 and BENCHMRK-2 studies have been described, as follows[62] :

- Q148K/R/H (25-fold decrease in susceptibility)
- N155H (10-fold decrease in susceptibility)

The most common mutational sequence (Q148H/G140S) results in a greater than 100-fold decrease in susceptibility to raltegravir.[37] A third resistance pathway involving mutations at Y143C/H/R has also been described for raltegravir but is uncommon.[63] Secondary mutations (L74M/R, E92Q, T97A, E138A/K, G140S/A, V151I, G163R, H183P, Y226D/F/H, S230R, D232N) confer additional resistance.[63]

Preliminary findings from clinical studies show that high-level resistance to elvitegravir is associated with mutations at E92Q in combination with E138K, Q148K/R/H, or N155H, leading to a 150-fold loss of susceptibility. Resistance patterns involving Q148H/G140S and Q148R/G140S demonstrate resistance to both elvitegravir and raltegravir, suggesting cross-resistance is likely.[64]

Pharmacokinetics

Raltegravir exhibits rapid absorption and may be taken with or without food. Its terminal half-life of 10-12 hours supports twice-daily administration (400 mg twice daily). Sex-related differences in pharmacokinetics (longer half-life in women, lower

C_{min} in men) have been observed but are not thought to be clinically significant. Raltegravir is 83% bound to plasma proteins and is a substrate for P-glycoprotein; the extent of penetration into the CNS remains to be determined.

Metabolism occurs through uridine diphosphate glucuronyl transferase 1A1 (UGT1A1). Dosage adjustment is not required in patients with renal insufficiency or mild-to-moderate hepatic impairment. Raltegravir exhibits low potential to affect the metabolism of other drugs; however, other antiretroviral agents may alter the metabolism of raltegravir.

Antacids may decrease absorption by divalent cation binding, but no interaction with gastric acid suppressants (proton pump inhibitors, H2 antagonists) is expected. A relationship between raltegravir serum concentrations and viral suppression has not been established.[65, 66, 67]

Elvitegravir is administered with low-dose ritonavir (100 mg) to reduce its first-pass metabolism and systemic clearance. Ritonavir coadministration results in a 20-fold increase in systemic exposure and a terminal half-life of 10-13 hours. Elvitegravir is metabolized through CYP3A4 and UGT1A1/UGT1A3. Less than 7% is eliminated renally; therefore, the likelihood that dosing adjustments will be necessary in patients with renal insufficiency who receive elvitegravir is low.

Drug-drug interactions with other medications are likely because of ritonavir coadministration. As with raltegravir, antacids may decrease absorption by divalent cation binding, but no interaction with gastric acid suppressants is expected. In dose-ranging studies, low elvitegravir trough concentrations have been associated with virologic failure in some patients.[67, 68, 69]

Adverse events

Common adverse effects observed in clinical studies of raltegravir include gastrointestinal effects (nausea, diarrhea) and headache. Laboratory abnormalities occurred at a frequency similar to other therapy in phase III studies and include grade 3-4 elevations in levels of alanine aminotransferase and aspartate aminotransferase, serum cholesterol and triglycerides, and amylase and lipase.

Elevations in creatine kinase levels (grade 2-4) were observed with raltegravir in phase III studies, along with rare cases of myopathy and rhabdomyolysis.[70, 71] Raltegravir should be used with caution in patients receiving other medications that may increase the risk for myopathy and rhabdomyolysis.[71]

A relative risk of malignancy of 1.2 cases per 100 patient-years (95% CI, 0.4-4.1) has been reported in phase II and phase III clinical studies of raltegravir and requires continued surveillance.[70] Gastrointestinal effects (nausea, diarrhea), fatigue, and headache have been most commonly observed with elvitegravir in limited clinical studies to date.[68]

Fusion Inhibitors

Fusion inhibitors (FIs) were the first class of antiretroviral medications to target the HIV replication cycle extracellularly and received accelerated FDA approval in 2003. Their unique mechanism of action provides additional options for therapy in patients who are highly treatment resistant.

The use of fusion inhibitors has been limited, however, because of the production time and costs, limited coverage from insurance companies and HIV drug-assistance programs (HDAPs), inconvenient administration (subcutaneous injection), and adverse effect profile. The discovery of additional antiretroviral classes and medications with activity against highly resistant viral strains has further limited the utility of the fusion inhibitors. Currently, enfuvirtide (Fuzeon) is the only product marketed in this class.

Mechanism of action

Fusion inhibitors act extracellularly to prevent the fusion of HIV to the CD4 or other target cell. Enfuvirtide blocks the second step in the fusion pathway by binding to the HR1 region of glycoprotein 41 (gp41). This mechanism does not allow HR1 and HR2 to fold properly, thereby preventing the conformational change of gp41 required to complete the final step in the fusion process.[72, 73]

Resistance

Resistance to enfuvirtide has been well described and occurs in the HR1 domain of gp41. Amino acid substitutions occur in the 36-45 regions and result in significant loss of enfuvirtide activity.[74]

The risk of resistance can be minimized by combining enfuvirtide with other antiretroviral agents that display genotypic or phenotypic activity, which is now more easily achieved with the availability of second-generation nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) and new antiretroviral classes (eg, integrase strand-transfer inhibitors [INSTIs] and CCR5 inhibitors).[75, 76] Cross-resistance with other antiretroviral agents has not been demonstrated to date.

Pharmacokinetics

Enfuvirtide therapy requires twice-daily subcutaneous injection. It has not been shown to influence the metabolism of concomitant medications through the cytochrome P450 system.

Dose adjustments are not required in patients with renal insufficiency or mild-to-moderate hepatic insufficiency. Limited dosing data exist for patients with advanced liver disease; therefore, enfuvirtide should be used with caution in patients with hepatic decompensation.[6, 77]

Adverse events

Most patients receiving enfuvirtide experience injection-site reactions, increasing drug discontinuation rates. Manifestations include subcutaneous nodules, erythema, pruritus, pain, and ecchymoses. Other adverse effects that occur to a lesser extent include diarrhea, nausea, and fatigue. Hypersensitivity reactions have been described but are rare. Enfuvirtide has been associated with an increased risk for bacterial pneumonia, but causality has not been established.[75, 76]

Chemokine Receptor Antagonists

In August 2007, maraviroc (Selzentry) was approved by the FDA and was the first medication in a novel class of antiretroviral agents termed chemokine receptor 5 (CCR5) antagonists. It joins the fusion inhibitors (FIs) as another type of agent under the general antiretroviral treatment class of HIV-entry inhibitors.

Mechanism of action

The method by which HIV binds to CD4 cells and ultimately fuses with the host cell is a complex multistep process, which begins with binding of the gp120 HIV surface protein to the CD4 receptor. This binding induces a structural change that reveals the V3 loop of the protein. The V3 loop then binds with a chemokine coreceptor (principally either CCR5 or CXCR4), allowing gp41 to insert itself into the host cell and leading to fusion of the cell membranes.

Maraviroc is a small molecule that selectively and reversibly binds the CCR5 coreceptor, blocking the V3 loop interaction and inhibiting fusion of the cellular membranes. Maraviroc is active against HIV-1 CCR5 tropic viruses. It has no activity against CXCR4 tropic or dual/mixed tropic virus.[78]

Resistance

Although experience with maraviroc is limited, treatment failure due to resistance has been observed. Resistance appears to occur via one of two mechanisms. The first mechanism is most likely through amino acid substitutions in the V3 loop of gp120. Although the specific mutations associated with resistance have not yet been described, they appear to allow HIV binding to the coreceptor despite the presence of maraviroc.

The second mechanism is not acquired resistance but rather the inability of phenotypic tropism assays to detect small quantities of CXCR4 virus that may be present, leading to overgrowth of CXCR4 virus in the presence of maraviroc and loss of viral control. The development of an enhanced tropism assay with higher sensitivity should minimize the frequency of this occurrence.[78, 79]

Genotypic assays can also be used to predict CCR5 and CXCR4 co-receptor tropism by sequencing the gp120 V3 loop. These assays have shown good-to-excellent concordance with phenotypic assays.[80, 81]

Pharmacokinetics

Maraviroc is approximately 75% protein-bound, primarily to albumin and $alpha_1$ acid glycoprotein. Its terminal half-life is 15-30 hours. Maraviroc is metabolized through CYP3A4 and is a substrate for the efflux pump p-glycoprotein. Dosage adjustment is required when maraviroc is administered in combination with potent inhibitors or inducers of CYP3A4.[78] See Table 1.[6]

Adverse events

Adverse events reported at a higher frequency than placebo in clinical studies include the following:

- Cough
- Pyrexia
- Upper respiratory tract infections
- Rash
- Musculoskeletal symptoms
- Abdominal pain
- Dizziness

The rate of discontinuation due to adverse effects was similar to that found with placebo (4.9% and 5.3%, respectively). Postural hypotension is a dose-limiting effect that was discovered early in the development of maraviroc. In pooled analysis, postural hypotension occurred only in patients who received maraviroc at doses that exceeded 600 mg/day. The manufacturer warns that severe hepatotoxicity has been reported with maraviroc; caution should be used when maraviroc is administered to any patient predisposed to hepatic impairment.[78]

DHHS Treatment Guidelines

Goals of therapy

The US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS ART Guidelines) issues recommendations for the administration of antiretroviral therapy.[6] Guidelines are based on results of clinical studies and expert opinion and are updated on an ongoing basis.

Separate guidelines address antiretroviral treatment for pregnant women, children, and individuals with potential occupational (eg, health care industry) and nonoccupational (eg, high-risk sexual encounters) exposure to HIV. Guidelines for antiretroviral treatment initiation in adults are also available from the International AIDS Society and the World Health Organization (WHO).

The discussion of antiretroviral treatment strategies in this article focuses on recommendations from the DHHS Panel.

The DHHS ART Guidelines present the following 5 overarching goals for therapy:

- Reduce HIV infection–related morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic function
- Maximally and durably suppress viral load
- Prevent vertical HIV transmission

Suppression of viremia also has the potential to reduce cardiovascular, renal, and hepatic events thought to be related to ongoing inflammation and immune activation from uncontrolled viremia. The risk for both AIDS-related and non–AIDS-associated malignancy may also be reduced by improved immunity.[6]

Treatment-naive patients

Indications for initiating antiretroviral therapy

The DHHS ART Guidelines recommend that therapy should be initiated in all patients irrespective of CD4 count to decrease the risk for HIV disease progression, non-HIV-related morbidity and mortality, and to prevent transmission of HIV infection. The decision to begin antiretroviral therapy, as well as the selection of the individual antiretroviral components, should be tailored to each patient, taking into account patient-specific variables and preferences. The patient's readiness and commitment to lifelong therapy should similarly be evaluated.Data from the START and TEMPRANO randomized trials have shown compelling evidence regarding the benefit of initiating ART in HIV infected individuals with high CD4-cell counts (>500 cells/mL), rather than defer treatment until CD4-cell counts decline.[82, 83] Findings from these studies showed a lower rate of death or severe HIV-related illness (eg, tuberculosis, Kaposi sarcoma, malignant lymphomas) in those who were treated early with ARTs compared to those that were deferred treatment until a lower CD4-cell count was observed.

Therapy options

Currently, 26 antiretroviral agents in 6 antiretroviral classes plus fixed-dose combination products are approved for use in the United States. These agents vary in their antiviral potency and administration requirements. It is currently recommended that antiretroviral therapy be initiated with 2 NRTIs in combination with an NNRTI, PI, or integrase inhibitor.[6]

In an attempt to simplify the selection of an initial regimen, the DHHS ART Guidelines have outlined preferred and alternative regimens for initiation in antiretroviral-naïve patients. There are now 5 recommended regimens for antiretroviral therapy (ART)-naive patients — 4 integrase strand transfer inhibitor (INSTI)-based regimens and 1 ritonavir-boosted protease inhibitor (PI/r)-based regimen. The five preferred regimens have evidence ratings of AI (ie, strong recommendation with data from randomized controlled trials). These recommendations are based on efficacy and safety of these combinations, as well as other factors, including ease of administration.[6]

Preferred regimens for ART-naïve patients include the following:

INSTI-based regimens

See the list below:

- Dolutegravir/abacavir/lamivudine (Triumeq; DTG/ABC/3TC) [a] —only for patients who are HLA-B*5701 negative
- Dolutegravir (DTG) + tenofovir DF/emtricitabine (Truvada; TDF/FTC) [a]
- Elvitegravir/cobicistat/tenofovir DF/emtricitabine (Stribild; EVG/c/TDF/FTC) —only for patients with pre-ART CrCl >70 mL/min
- Raltegravir (RAL) + tenofovir DF/emtricitabine (Truvada; TDF/FTC) [a]

PI/r-Based Regimen

See the list below:

- Darunavir/ritonavir (DRV/r) + tenofovir/emtricitabine (Truvada; TDF/FTC) [a]

[a] lamivudine (3TC) may be substituted for emtricitabine (FTC) or vice versa

Alternative regimens for ART-naïve patients include the following:

NNRTI-based Regimens

See the list below:

- Efavirenz/tenofovir DF/emtricitabine (Atripla; EFV/TDF/FTC) [a]
- Rilpivirine/tenofovir DF/emtricitabine (Complera; RPV/TDF/FTC) [a] —only for patients with pre-treatment HIV RNA < 100,000 copies/mL and CD4 cell count >200 cells/mm ^{3}

PI-based Regimens

See the list below:

- Atazanavir/cobicistat (Evotaz; ATV/c) + tenofovir/emtricitabine (Truvada; TDF/FTC) [a] — only for patients with pretreatment estimated CrCl ≥70 mL/min
- Atazanavir/ritonavir (ATV/r) + tenofovir DF/emtricitabine (Truvada; TDF/FTC) [a]
- Darunavir/cobicistat or darunavir/ritonavir (Prezcobix; DRV/c or DRV/r) +

abacavir/lamivudine (Epzicom; ABC/3TC) [a] —only for patients who are HLA-B*5701 negative
- Darunavir/cobicistat (Prezcobix; DRV/c) + tenofovir DF/emtricitabine (Truvada; TDF/FTC) [a] —only for patients with pretreatment estimated CrCl ≥70 mL/min

[a] lamivudine (3TC) may be substituted for emtricitabine (FTC) or vice versa

In a long-term study of treatment-naïve patients, raltegravir combined with tenofovir/emtricitabine delivered durable viral suppression and immune restoration that was at least equivalent to the combination of efavirenz and tenofovir/emtricitabine. In addition, fewer drug-related clinical adverse events and smaller elevations in lipid levels occurred in patients in the raltegravir combination group.[84]

Resistance

One study has reported that antiretroviral resistance can be detected in 6-16% of treatment-naive individuals.[6] Based on this possibility, DHHS guidelines recommend that resistance testing be performed in all patients with HIV infection at the onset of care.

Genotypes are generally the test of choice, as de novo resistance to NRTIs or NNRTIs is most commonly observed. Genotypes are also less costly and exhibit a shorter turnaround time. If the interval between entering care and beginning antiretroviral therapy is significant, it is generally recommended that the patient undergo testing with another genotype to assess any resistance acquired in the interim.[6]

Therapy selection

The antiretroviral regimen selected should be based on patient-specific factors and preferences. Factors to consider include associated comorbidities, the adverse-effect profiles of the medications being considered, the potential for pregnancy, adherence barriers, regimen convenience, and potential drug-food and drug-drug interactions. Resistance testing findings should also be considered in the initial regimen selection.

Certain agents require consideration of other factors (eg, HLA-B*5701 testing for abacavir hypersensitivity, pretreatment CD4 count for nevirapine) before their use.[6]

Treatment endpoints

Virologic endpoints for therapy include the following:

- One $\log_{10}$ decline in HIV-1 RNA by 2-8 weeks
- Fewer than 50 HIV-1 RNA copies/mL by 16-24 weeks

If one of these endpoints is not met, the patient should be evaluated to determine whether nonadherence, drug intolerance, or resistance is a factor. Alteration of therapy may be necessary based on the specific circumstances.[6]

Treatment-experienced patients

Definition of treatment failure

Although success with antiretroviral therapy has greatly improved with the introduction of more potent and well-tolerated medications, treatment failure remains an important challenge for clinicians. Failure of antiretroviral therapy is defined under the following circumstances[6] :

- Virologic failure (suboptimal viral suppression or loss of suppression [>50 HIV-1 RNA copies/mL])
- Immunologic failure (failure to achieve or maintain CD4 cell count recovery despite effective viral suppression)
- Clinical disease progression (development of new opportunistic infections or neoplasms despite apparent CD4 count recovery)

Treatment failure is often due to multiple factors. The identification of potential contributing factors is important so that corrective measures can be instituted to improve the likelihood of success with new therapy. Common factors that contribute to treatment failure include the following:

- Nonadherence
- Drug toxicity
- Potency of the antiretroviral regimen
- Drug-drug interactions leading to suboptimal drug concentrations
- Pre-existing drug resistance prior to institution of antiretroviral therapy
- Development of resistance

Virologic failure is the most common reason for treatment failure. Virologic failure in the DHHS ART Guidelines is defined as incomplete virologic suppression or viral rebound, leading to inability to maintain viral suppression.[6] Different definitions of virologic failure are applied depending on when the antiretroviral regimen was initiated, as follows:

- More than 400 HIV-1 RNA copies/mL after 24 weeks
- More than 50 HIV-1 RNA copies/mL after 48 weeks
- Repeatedly detectable viremia after prior viral suppression (ie, < 50 HIV-1 RNA copies/mL)

No consensus on the management of virologic failure exists. One approach is to change antiretroviral therapy when HIV-1 RNA is repeatedly detectable (>50 copies/mL on 2 consecutive measurements). A more conservative approach would be to change therapy once viremia exceeds some predefined level (eg, 1,000-5,000 copies/mL). A potential disadvantage to this approach is that additional resistance

mutations may be selected during this period of viremia. The availability of other antiretroviral therapy options often dictates which approach should be taken.[6]

The identification and management of treatment failure due to immunologic failure is less clear. No standard definition for immunologic failure exists. In some instances, the inability to surpass predefined thresholds (CD4 count >350 cells/µL) over a specified period when CD4 counts are expected to plateau (4-7 y) has been labeled immunologic failure. In other instances, a lack of CD4 cell count increase from baseline (eg, 100 cells/µL) over a defined period has also been considered a failure.[6]

Risk factors associated with immunologic failure include the following:

- Low CD4 count (< 200 cells/µL)
- Comorbidities (eg, malignancy, viral coinfection)
- Older age
- NRTIs (zidovudine, tenofovir-didanosine)
- Other medications (eg, corticosteroids, chemotherapy, pegylated interferon)
- Ongoing immune activation
- Loss of immune system regenerative potential

The implications for persistently impaired CD4 recovery in the individual patient need to be balanced with existing treatment options. Considerations include the following[6] :

- Patients with CD4 cell counts that exceed 350-500 cells/µL are at a low risk for non–AIDS-related clinical events
- Patients with CD4 cell counts of less than 200 cells/µL are at greatest risk for both AIDS-related and non–AIDS-related events
- Replacement of individual antiretroviral components (eg, NNRTI to protease inhibitor) can be attempted provided that complete viral suppression is present, but this strategy remains unproven
- Addition of a single antiretroviral agent to the existing regimen has not been shown to be effective
- The use of immune stimulants (eg, interleukin-2, growth hormone) is presently recommended only in the context of a clinical trial

Likewise, decisions to alter antiretroviral therapy in patients with disease progression are determined based on clinical severity and existing treatment options.

Therapy selection

Antiretroviral activity and durability improves with the addition of at least 2 or, optimally, 3 fully active agents to an optimized background regimen. The selection of individual agents for an optimized background regimen should be based on the antiretroviral treatment history, genotypic and/or phenotypic resistance results, drug-drug interaction potential, and medication intolerance, with the goal of maximizing antiviral activity and adherence.

Divergence from the strategy of using 2 NRTIs with either an NNRTI or a protease inhibitor is typically necessary as the extent of drug resistance increases. Four to six drug regimens are commonly used in patients with extensive drug resistance in order to increase the degree of activity.[6]

The introduction of new antiretroviral agents has broadened the number of active agents available for treatment of patients with infection due to resistant HIV and has improved the success rate of therapy. Raltegravir, tipranavir, darunavir, enfuvirtide, maraviroc, and etravirine are frequently considered for use. Limited information exists regarding optimal combinations of these agents for treatment, as selection is often based on resistance testing results, prior treatment history, and intolerance.[6]

Enfuvirtide is highly effective in the treatment of antiretroviral therapy–experienced patients but requires subcutaneous injection twice daily and is associated with injection-site reactions.

Darunavir and tipranavir typically retain activity in the presence of multiple protease inhibitor mutations.

The use of tipranavir has been hindered by the potential for interaction with other antiretroviral agents, hepatotoxicity, and reports of intracranial bleeding events.

Raltegravir has been demonstrated to be highly active in patients with extensive drug resistance in short-term studies (48 weeks) and is well-tolerated.

Etravirine is most effective when combined with other active agents but may cause drug-drug interactions with other antiretroviral agents.

The role of maraviroc in this setting has been limited because of the high frequency of dual/mixed-tropic or CXCR4-tropic virus in patients with more long-standing HIV infection and the necessity for expensive tropism assay pretesting.

Goals of therapy

The goals of therapy in treatment-experienced patients are the same as in treatment-naive patients.[6] With the introduction of newer agents, suppression of viremia to below the limit of assay detection (< 48 copies/mL) is now achievable in many patients who harbor drug-resistant viral strains.

Genotypic or phenotypic resistance testing should be used to assist with selection of appropriate therapy and should be obtained while patients remain on their previous therapy or within 4 weeks of discontinuation to improve the sensitivity of results. Phenotypic testing is generally added to genotypic testing when complex drug resistance mutation patterns, especially to protease inhibitors, are confirmed or suspected.[6]

Virologic endpoints for therapy include the following:

- One log $_{10}$ decline in HIV-1 RNA by 8 weeks
- Fewer than 400 HIV-1 RNA copies/mL by 24 weeks
- Fewer than 50 HIV-1 RNA copies/mL by 48 weeks

If one of these endpoints is not met, the patient should be evaluated to determine whether nonadherence, drug intolerance, or resistance is a factor.

Special populations

Pregnancy

Antiretroviral therapy is recommended in all pregnant women with HIV infection regardless of viral load or CD4 count. Independent of viral load, antiretroviral therapy has been shown to decrease the likelihood of mother-to-child transmission. The goal of therapy is to achieve maximal virologic suppression to minimize the transmission risk. It is recommended that all women initiating therapy for the first time or those receiving therapy who have a detectable viral load undergo genotypic resistance testing to guide therapy selection.

Preferred agents include the following:

- NRTI - Zidovudine, lamivudine
- NNRTI - Nevirapine
- Protease inhibitor (PI) - Lopinavir/ritonavir

Antiretroviral therapy should consist of two NRTIs with either an NNRTI or PI, guided by resistance testing. Lopinavir/ritonavir in combination with zidovudine/lamivudine is preferred in most cases. Efavirenz is not recommended during the first trimester because of significant teratogenicity in primate studies and should be used during the second and third trimesters only if it offers clear benefit over other alternatives.

A retrospective cohort study reviewed the records of 3,273 HIV-positive women receiving prenatal care in Malawi and Mozambique from July 2005 to December 2009. Patients were treated with triple antiviral therapy during pregnancy until 6 months postpartum for prevention of vertical transmission. Regardless of CD4 count, ART provided a protective effect against mortality, fetal demise, and premature birth.[85]

PI-based HAART is associated with increased preterm delivery (21.4% versus 11.8% with NRTI therapy) but not with increased infant hospitalizations or mortality.[86]

Caution should be used with nevirapine regimens owing to observed hepatic failure and death in a small number of patients. The risk for nevirapine-related toxicity is increased with CD4 counts above 250/µL in women; therefore, nevirapine should be used only in women with higher CD4 counts if the benefit outweighs the risk.

The OCTANE study showed that ritonavir-boosted lopinavir plus tenofovir–emtricitabine was superior to nevirapine plus tenofovir–emtricitabine for initial antiretroviral therapy in women with prior exposure to peripartum single-dose nevirapine (but not in those without prior exposure).[87] Zidovudine should be included in all regimens unless its use is precluded by severe toxicity or documented resistance.

Regardless of the antenatal regimen, zidovudine should be administered by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks following birth. More detailed information regarding treatment of pregnant women with HIV infection is included in guidelines from the U.S. Public Health Service for prevention of perinatal HIV transmission.[88] Providers are encouraged to report all cases of perinatal antiretroviral exposure to the Antiretroviral Pregnancy Registry.

Postexposure prophylaxis following occupational HIV exposures

Postexposure prophylaxis (PEP) has been demonstrated to reduce the risk of HIV infection when administered soon after exposure. The risk for HIV infection is determined based on the exposure type (percutaneous, mucous membrane, intact skin), severity of exposure (small or large volume, superficial or deep injury), and source status (known or unknown HIV status). Postexposure prophylaxis is recommended for exposures from a documented HIV source and is considered optional when the HIV status of the source individual is unknown.

For low-risk exposures (eg, mucous membrane), a 2-drug (basic) regimen is recommended. For high-risk exposures (eg, percutaneous needle stick), a 3-drug (expanded) regimen is recommended. Ideally, therapy should be started as soon as possible after exposure (within hours) and continued for 28 days.

The following are the preferred basic regimens:

- Zidovudine plus lamivudine
- Zidovudine plus emtricitabine
- Tenofovir plus lamivudine
- Tenofovir plus emtricitabine

The preferred expanded regimen is the basic regimen plus lopinavir/ritonavir.

A consultation with an expert should be sought when antiretroviral therapy for postexposure prophylaxis is considered, especially when the antiretroviral treatment history of the source individual is known. Additional information on treatment selection and management can be found in the US Public Health guidelines for occupational HIV exposure.[89]

Postexposure prophylaxis following nonoccupational HIV exposures

Nonoccupational exposure to HIV includes any exposure to potentially infectious bodily fluids and tissues not secondary to job duties. These exposures include but

are not limited to sexual contact and the sharing of injection-drug equipment.

Data from animal studies, perinatal transmission studies, experience with occupational post-exposure prophylaxis, and observational studies support the premise that initiation of a brief course of antiretroviral therapy after nonoccupational exposure may decrease the likelihood of HIV transmission.[90]

It is recommended that patients who present 72 hours or sooner after a substantial-risk HIV exposure involving an HIV-infected source be offered postexposure prophylaxis consisting of 3 antiretroviral agents. The risk is based on the type of exposure. If the HIV status of the source is unknown, each case should be determined individually based on risk.[90]

Substantial risk criteria include the following:

- Site of exposure - Vagina, rectum, eye, mouth, or other mucous membrane, nonintact skin, or percutaneous contact
- Infectious material - Blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood
- Source status - Known HIV infection in the source
- Negligible risk criteria include the following:
- Site of exposure - Vagina, rectum, eye, mouth, or other mucous membrane, intact or nonintact skin, or percutaneous contact
- Infectious material - Urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood
- Source status - Regardless of the known or suspected HIV status of the source

Postexposure prophylaxis is not recommended in patients who present more than 72 hours after exposure or who have exposures deemed to represent a negligible risk. If antiretroviral therapy is initiated, it should be continued for 28 days.[90]

The preferred regimens are as follows:

- Efavirenz plus lamivudine or emtricitabine plus zidovudine or tenofovir
- Lopinavir/ritonavir plus lamivudine or emtricitabine plus zidovudine

Adolescents

Adolescents with HIV infection represent a heterogenous patient population. This population includes newly infected patients and long-term survivors who were infected perinatally or through blood products. Adult treatment guidelines are usually appropriate in postpubertal adolescents. Similarly, patients infected with HIV via intravenous drug use or sexual encounters should be managed according to adult guidelines.

Antiretroviral dosing should be based on the Tanner staging of puberty. Patients in stage I or II should receive medications according to pediatric schedules; those in late puberty (stage V) should undergo management according to adult guidelines. Few data provide guidance for dosing in adolescents who fall in stages III and IV. Close monitoring for efficacy and toxicity is imperative, regardless of the dosing schedule used to implement therapy.[6]

Patients with acute HIV infection

Limited data are available to define the role of treatment in patients with acute HIV infection. The potential benefits of initiating treatment during acute infection remain theoretical. Treating acute infection may decrease the severity of acute disease, lower the level of chronic viremia following symptom resolution, decrease viral mutation, preserve immune function, and reduce transmission.

If the patient and provider decide to implement treatment based on these potential benefits, combination therapy should be initiated similar to that administered in patients with chronic infection. It is recommended that protease inhibitor–based regimens be considered owing to the lower incidence of resistance to these agents in treatment-naïve patients. Providers may want to consider enrolling these patients into a clinical trial evaluating the natural history and the role of antiretroviral treatment in acute HIV infection.[6]

Coinfection

A significant amount of morbidity and mortality in persons with HIV infection results from coinfection with *Mycobacterium tuberculosis* (MTB), hepatitis B virus (HBV), or hepatitis C virus (HCV). Each of these infections is more difficult to manage in patients with HIV infection because of the accelerated rate of disease progression, lower treatment response rates, drug-drug interactions, and additive toxicities that result from concomitant therapies. Furthermore, HIV treatment is more imperative in the presence of coinfection, leading to initiation of antiretroviral therapy at higher CD4 counts than in patients with HIV monoinfection.

The antiretroviral treatment sequencing strategy for each type of coinfection is challenging and must be tailored to individual patient-specific needs to provide the best possible outcome and to restore quality of life.

Tuberculosis

The overall rate of morbidity and mortality associated with *M tuberculosis* coinfection in patients with HIV infection is significant. Worldwide, estimates of the mortality rate due to *M tuberculosis* infection in the presence of HIV infection are 13%; however, such rates have significantly decreased in the United States because of the aggressive implementation of public health and hospital *M tuberculosis* programs.[91]

Nonetheless, significant overlap exists in the patient populations who are exposed to *M tuberculosis* and are at risk for HIV infection. Disease progression rates of each are accelerated with coinfection and require swift and aggressive management strategies. However, patients are not routinely screened for tuberculosis prior to the

initiation of antiretroviral therapy. A cohort study of HIV-infected patients identified risk factors for developing tuberculosis after HAART initiation in an effort to focus screening efforts. Results suggest patients with CD4 counts < 200 cells/µL or increased HIV-1 RNA, persons of nonwhite race or Hispanic ethnicity, and patients with a history of injection drug use should be targeted for tuberculosis screening.[92]

Current recommendations suggest that treatment for *M tuberculosis* infection and HIV infection be initiated separately because of additive adverse effects and overlapping toxicities; however, the ideal time frame between the two is less well-defined.[93]

Factors to consider with treatment sequencing for HIV and *M tuberculosis* coinfection include when to initiate each therapy and how to manage drug-drug interactions, adverse effects, and additive toxicities. In treatment-naïve patients, the focus of therapy should be directed initially toward *M tuberculosis* infection, but the implications for subsequent antiretroviral therapy must be considered in order to avoid or manage pending drug-drug interactions.

Treatment selection for latent or active *M tuberculosis* infection is generally straightforward; however, significant drug-drug interactions are possible with antiretroviral medications when a rifamycin is included in the treatment plan because of their strong inductive effects on the cytochrome P450 system.[94] Rifabutin is usually selected over rifampin because of its less-potent metabolic induction when antiretroviral therapy is required, but dose adjustments are necessary when protease inhibitors and NNRTIs are administered concomitantly.

Delaying antiretroviral therapy in treatment-naïve patients is controversial but necessary in order to assess potential side effects and toxicities (eg, gastrointestinal effect, hepatotoxicity) that are similar with each therapy. Current guidelines recommend a delay in antiretroviral therapy for 2-8 weeks after the initiation of *M tuberculosis* infection therapy, with consideration given to the potential consequences of antiretroviral therapy deferral in each patient.

Several studies indicate that initiating HAART 2 weeks after the start of tuberculosis treatment significantly improves survival among HIV-infected adults with CD4+ T-cell counts of 200 per cubic millimeter or lower. Starting stavudine, lamivudine, and efavirenz after 2 weeks of tuberculosis treatment instead of 2 months improved mortality from 27% to 18% in one study with 661 patients.[95] In another study, earlier HAART was associated with a lower rate of new AIDS-defining illness and death (27% vs 16%) in 881 patients with CD4+ T-cell counts of less than 50 per cubic millimeter.[96]

A study with 642 ambulatory patients showed a decreased incidence rate of AIDS or death with 9 and 27 cases per 100 person-years in patients with CD4+ T-cell counts of less than 50 per cubic millimeter (1 month vs 2.5 months).[97] However, the risk of immune reconstitution inflammatory syndrome was significantly increased in the earlier HAART group (2.5% vs 3.6%).

In patients currently receiving antiretroviral therapy, *M tuberculosis* infection therapy should be initiated as soon as possible, with similar consideration given to the potential for drug-drug interactions. Antiretroviral therapy recommendations for patients receiving treatment for *M tuberculosis* infection are discussed below.[6, 93]

For treatment-naïve (antiretroviral therapy initiation within the *M tuberculosis* infection treatment period), recommendations are as follows:

- Protease inhibitor–based regimen - Recommended to use ritonavir-boosted regimen
- NNRTI-based regimen - No dose adjustments required for efavirenz or nevirapine; limited data for etravirine
- Maraviroc-containing regimen - Potential for altered serum levels (dose determined by concomitant antiretroviral agents in the presence of rifabutin)

For treatment-experienced (currently receiving antiretroviral therapy), recommendations are as follows for protease inhibitor–containing regimens:

- Unboosted - Change to ritonavir-boosted form
- Currently boosted - No dose adjustment required

For treatment-experienced (currently receiving antiretroviral therapy), recommendations are as follows for NNRTI-containing regimens:

- Efavirenz or nevirapine - No dose adjustments required
- Etravirine - If not given concomitantly with boosted protease inhibitor, consider alternative
- Maraviroc - Limited data
- Hepatitis B virus infection

Approximately 10% of individuals infected with HIV have HBV coinfection.[98] Treatment for each disease can be challenging because of accelerated disease progression and lower treatment response rates for HBV infection and increased rates of hepatotoxicity with antiretroviral therapy. Patients with HIV and HBV coinfection often have higher HBV DNA, lower HBeAg seroconversion rates, and an increased risk of liver-related mortality.[99, 100, 101, 102]

Additionally, acute hepatic flares due to antiretroviral therapy are more likely in the presence of HBV owing to the compromised state of the liver and immune reconstitution reactions that can occur with treatment initiation at low CD4 counts.[100] Nonetheless, overlapping therapies exist and are integrated into a treatment regimen that is optimal for both HIV infection and HBV infection.

The goals of therapy for HIV and HBV coinfection reflect those of HIV and HBV monoinfection. The sequencing of therapy is patient-specific and is guided by criteria for each disease. Treatment for both can be successfully combined and should include NRTIs that possess activity against both viruses (tenofovir, lamivudine, emtricitabine).

Most often, a 3-drug combination is recommended in patients with HIV and HBV coinfection when treatment is indicated for either disease in order to prevent the development of antiretroviral drug resistance. Both HIV and HBV can acquire resistance to the NRTIs, so therapy must be tailored to retain virologic control.

If either virus acquires resistance, additional medications should be added to the current regimen rather than substituted in order to maintain virologic control of the remaining drug-susceptible virus. When HBV acquires resistance in the presence of HIV, other NRTIs that lack HIV activity (adefovir, telbivudine) can be added to the existing HBV regimen; however, entecavir should be used only in coinfected individuals with longstanding HIV RNA suppression because of its activity against HIV and the proposed risk of HIV drug resistance.

In patients receiving HBV treatment without concomitant HIV therapy, pegylated interferon, adefovir, or telbivudine is recommended. Antiretroviral therapy recommendations in patients with HIV and HBV coinfection are discussed below.[100]

If only HIV treatment is required (and not HBV), recommendations are as follows:

- NRTI backbone should include tenofovir plus emtricitabine or lamivudine: Combination actively treats both HIV and HBV
- Third agent for HIV (patient- or provider-specific choice that minimizes hepatotoxicity potential)

If only HBV treatment is required (and not HIV), recommendations are as follows:

- HBV DNA greater than 2000 IU/mL: Antiretroviral therapy must be initiated to prevent HIV resistance and should include tenofovir plus emtricitabine or lamivudine for the NRTI backbone
- HBV DNA less than 2000 IU/mL: Pegylated interferon alpha-2a 180 µg once weekly for 48 weeks, Adefovir, Telbivudine

Hepatitis C virus infection

Approximately 25% of persons with HIV infection are coinfected with HCV.[103, 104] HCV infection in the presence of HIV infection progresses to cirrhosis or end-stage liver disease twice as quickly as in HCV monoinfection.[105]

Treatment outcomes, as measured by end-of-treatment response and sustained virologic response rates, are also lower in patients with HCV and HIV coinfection.[106, 107] Although HIV disease progression has not been directly linked to HCV coinfection, it is significantly influenced by the lower rise in CD4 counts once antiretroviral therapy is initiated and the increased risk for hepatotoxicity with antiretroviral therapy.

Drug interactions with antiretroviral therapy and standard HCV therapy have been demonstrated with the NRTIs and ribavirin. Such interactions can produce significant toxicities and/or reduce the likelihood of response to HCV therapy. Sequencing of therapy usually begins with treatment of HIV infection; however, when a patient has not met treatment criteria or is unable to tolerate antiretroviral therapy, HCV treatment should be considered.

Ideally, patients with HCV and HIV coinfection should have a CD4 count that exceeds 200/µL prior to HCV treatment initiation in order to improve tolerance and response to therapy; however, sufficient CD4 recovery is not within reach in some cases.[6, 100] In these situations, HCV therapy should be initiated rather than delayed further because of the urgency to reduce HCV disease progression.[100]

Treatment options for HCV therapy are presently limited to combination therapy with pegylated interferon and ribavirin. Response rates are lower in coinfected patients, and extended treatment durations (eg, 48-72 weeks) are often recommended.[106, 107, 108]

Therapy for HIV consists of the standard 3-drug regimen, but drug interactions between antiretroviral agents and ribavirin and overlapping toxicities can further complicate treatment selection. Close monitoring of serum transaminases during combined antiretroviral therapy and HCV therapy is warranted because of the increased risk of hepatotoxicity.

Drugs that interact or add toxicities with ribavirin include the NRTIs didanosine, zidovudine, and abacavir. The combination of didanosine and ribavirin is contraindicated owing to increased intracellular concentrations of didanosine that significantly increase the risk of life-threatening lactic acidosis and pancreatitis.[109]

Zidovudine and ribavirin can cause additive anemia and should be considered only in patients with a stable hemoglobin concentration. Lower HCV treatment response rates have been described in coinfected patients receiving abacavir-containing antiretroviral therapy regimens in 2 clinical trials.[110, 111]

When early virologic response rates and sustained virologic response rates were compared between abacavir-containing regimens and other nucleoside regimens, poorer outcomes reaching statistical significance were demonstrated in the abacavir group.

Although the ribavirin and abacavir interaction has not been fully described, both are guanosine analogs and hypothesized to have competitive phosphorylation that can result in lower ribavirin concentrations. Tenofovir, on the other hand, has been shown to improve HCV treatment response rates when included in the antiretroviral therapy regimen and combined with ribavirin.[111]

Although guidelines for the use of abacavir and tenofovir in combination with HCV therapy have not been implemented, consideration should be given to these more recent findings. An abacavir-containing regimen should be avoided in coinfected patients who are candidates for HCV therapy until further data become available.

Pre-exposure prophylaxis

A multinational study, called the Pre-exposure Prophylaxis Initiative (iPrEx) trial, found that once-daily emtricitabine plus tenofovir disoproxil fumarate (FTC-TDF) reduced the risk of acquiring HIV by 44% in a study population of high-risk, HIV-negative men or transgender women who have sex with men.[112]

Currently, no data are available on the benefits of FTC-TDF in heterosexuals or injection drug users. The Centers for Disease Control and Prevention (CDC) will determine how to most effectively use FTC-TDF in combination with other prevention strategies to reduce new HIV infections. The CDC, National Institutes of Health (NIH), and other institutions are also conducting trials to determine the safety and effectiveness of pre-exposure prophylaxis (PrEP) for these populations.[113, 114]

Preexposure prophylaxis (PrEP) may be part of comprehensive HIV prevention services in which HIV-negative people who are at high risk, take antiretroviral medication daily to try to lower their chances of becoming infected with HIV if they are exposed to it. PrEP consists of taking the combination drug, emtricitabine 200 mg and tenofovir 300 mg (Truvada), once daily.[115, 116]

Compliance is essential. In studies, the level of protection varied widely depending on how consistently participants used PrEP. Among those whose data (based on self-reports, bottles dispensed, and pill counts) indicate use on 90% or more days, HIV risk was reduced by 73%. Among those whose adherence by the same measure was less than 90%, HIV risk was reduced by only 21%. Comprehensive prevention services are also required (ie, monthly HIV testing, condom provision, counseling, and management of other sexually transmitted infections).

To date, PrEP has been shown to be effective only in men who have sex with men (MSM) and transgendered women who have sex with men. Studies are underway to evaluate whether PrEP is safe and effective in reducing HIV infection among heterosexual men and women as well as injection drug users, but those results are not yet available.

HIV-discordant couples

A *Cochrane Database of Systematic Reviews* analysis of 7 observational studies found that ART is very potent for the prevention of HIV in couples in which only one partner is infected with the virus. Results show that in serodiscordant couples, uninfected partners of infected individuals being treated with antiretroviral drugs have a 5 times' lower risk of contracting HIV compared to uninfected partners of infected individuals not receiving treatment.

Whether to initiate ART in this population at the time of diagnosis or at a specific CD4 or plasma viral load level is unclear. A large, randomized controlled trial addressing this question is scheduled to conclude in 2015.[117]

A multicontinent, randomized, controlled trial by the HIV Prevention Trials Network (HPTN) in 2011 evaluated early versus delayed antiretroviral therapy for HIV-infected patients with CD4 counts between 350 and 550/µL who were in stable sexual relationships with noninfected partners. Findings show that early initiation of antiretroviral therapy reduced transmission rates of the disease by 96%. Early therapy was also associated with a 41% reduction in the number of HIV-related clinical events.[118]

Tables of Antiretroviral Drug Interactions

Interactions between antiretroviral drugs are described in Table 2, below. Interactions between antiretroviral drugs and other drugs are described in Table 3, below.

For additional detailed information, see Drug Interactions with Antiretroviral Therapy or NIH Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Table 2. Drug Interactions Between Antiretroviral Agents[6] (Open Table in a new window)

Antiretroviral Agent	Interacting Antiretroviral Agent	Predicted Effect	Management
Atazanavir (ATV)	Tenofovir	↓ATV	Administer ATV 300 mg with ritonavir 100 mg
	Etravirine	↓ATV, ↑ETV	Do not coadminister
	Nevirapine (NVP)	↓ATV, ↑NVP	Do not coadminister
	Efavirenz	↓ATV	Administer ATV 400 mg with ritonavir 100 mg (treatment-naive); do not coadminister (treatment-experienced)
Abacavir (ABC)	Tipranavir	↓ABC	Avoid coadministration
Darunavir (DRV)	Lopinavir/ritonavir, saquinavir	↓DRV	Do not coadminister
Didanosine (ddI)	Tenofovir	↑ddI	Decrease ddI dose (250 mg qd)
Etravirine (ETV)	Tipranavir	↓ETV	Do not coadminister
Fosamprenavir (FPV)	Lopinavir/ritonavir, tipranavir	↓FPV	Do not coadminister

	Etravirine	↑FPV	Avoid coadministration
Indinavir (IDV)	Tipranavir	↓IDV	Do not coadminister
Lopinavir/ritonavir (LPV/r)	Efavirenz, nevirapine	↓LPV	LPV/r 500/125 mg bid (tablet) or 533/133 mg bid (liquid)
	Tipranavir	↓LPV	Do not coadminister
Maraviroc (MVC)	Efavirenz, etravirine	↓MVC	Increase MVC dose (600 mg bid)
	PIs (except tipranavir)	↑MVC	Decrease MVC dose (150 mg bid)
	Delavirdine	↑MVC	Decrease MVC dose (150 mg bid)
Nelfinavir (NFV)	Tipranavir	↓NFV	Do not coadminister
Saquinavir (SQV)	Tipranavir	↓SQV	Do not coadminister
Zidovudine (ZDV)	Tipranavir	↓ZDV	Avoid coadministration
Abbreviations: ART, antiretroviral therapy; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.			

Table 3. Representative List of Drug Interactions Between Antiretroviral Agents and Other Medications[6, 119, 120, 121] (Open Table in a new window)

Medication	Antiretroviral Agent	Predicted Effect	Management
Antacids	Raltegravir (RAL), elvitegravir (ETG)	↓RAL, ETG	Avoid concurrent administration
	Atazanavir (ATV)	↓ATV	Take ATV 2 h before or 1 h after antacids
	Tipranavir/ritonavir (TPV/RTV)	↓TPV	
Fluticasone	PIs, delavirdine	↑Fluticasone	Avoid coadministration
H2-antagonists (H2A)	Atazanavir (ATV)	↓ATV	Boosted ATV: Administer simultaneously or >10 h after H2A; do not exceed 40 mg famotidine dose equivalent bid (treatment-naive) or 20 mg bid (treatment-experienced) Unboosted ATV: Administer >2 h before or >10 h after H2A; do not exceed 20 mg famotidine dose equivalent bid (treatment-naive)
	Fosamprenavir (FPV)	↓APV	
	Rilpivirine (RPV)	↓RPV	Unboosted FPV: Administer FPV >2 h before H2A; consider RTV boosting RPV: Administer H2A either 12 h before or 4 h after RPV
Methadone	Boosted PIs, nelfinavir	↓Methadone	Monitor for withdrawal symptoms
PDE5 inhibitors (sildenafil, tadalafil, vardenafil)	PIs, delavirdine	↑PDE5 inhibitor	Begin with sildenafil 25 mg q48h Begin with tadalafil 5 mg; do not exceed 10 mg q72h Begin with vardenafil 2.5 mg; do not exceed 2.5 mg q72h
Phenytoin (PHT)	Lopinavir/ritonavir (LPV/r)	↓PHT, ↓LPV/r	Monitor PHT serum concentrations and HIV RNA
Proton pump inhibitors (PPIs)	Atazanavir (ATV)	↓ATV	PPIs not recommended with unboosted ATV or in ART-experienced patients. Do not exceed omeprazole 20 mg dose equivalent; separate dosing by 12 h (ART-naïve) TPV/RTV: Consider omeprazole dose increase with TPV/RTV RPV: Do not coadminister with
	Tipranavir/ritonavir (TPV/RTV)	↓Omeprazole (with TPV/RTV)	
	Rilpivirine (RPV)	↓RPV	

			PPIs
Rifabutin	PIs	↑Rifabutin	Decrease rifabutin dose to 150 mg qd-qod
	Efavirenz	↓Rifabutin	Increase rifabutin dose to 450 mg
	Rilpivirine (RPV), delavirdine (DLV)	↓RPV, DLV	Do not coadminister
Rifampin	PIs	↓PI	Do not coadminister; increased risk for hepatotoxicity
	NNRTIs	↓NNRTI	Do not coadminister with NVP, DLV, ETV, RPV EFV: Consider EFV dose increase to 800 mg/d for patients >60 kg
	Maraviroc (MVC)	↓MVC	Do not coadminister
	Raltegravir (RAL)	↓RAL	Rifampin is a strong UTG1A1 inducer; increase RAL dose to 800 mg bid
Salmeterol	PIs	↑Salmeterol	Avoid coadministration; increased risk of QT interval prolongation
Statins (simvastatin, lovastatin, pitavastatin)	PIs, delavirdine	↑Statin	Do not coadminister
	NNRTIs (except delavirdine)	↓Statin	Adjust statin dose according to response
Voriconazole	Boosted PIs	↓Voriconazole	Do not coadminister
	Efavirenz	↓Voriconazole ↑EFV	Increase voriconazole maintenance dose to 400 mg bid and decrease EFV dose to 300 mg/d
Warfarin	Efavirenz, delavirdine, etravirine	↑Warfarin	Monitor INR and adjust warfarin dose accordingly
	Boosted PIs, nevirapine	↓Warfarin	Monitor INR and adjust warfarin dose accordingly

Abbreviations: INR, international normalized ratio; PDE5, phosphodiesterase 5 inhibitors; PIs, protease inhibitors.

Pharmacokinetic Enhancers (Boosting Agents)

Cobicistat (Tybost) is a CYP3A inhibitor. As a single agent, it is indicated to increase systemic exposure of atazanavir or darunavir (once-daily dosing regimen) in combination with other antiretroviral agents. It is also a component of elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild).

Cobicistat may be used for treatment-naïve or experienced patients (without darunavir resistance-associated substitutions). The dosage is 150 mg PO once daily plus atazanavir 300 mg PO once daily or darunavir 800 mg PO once daily.

Ritonavir is also a potent CYP3A4 inhibitor that is in many combination productions and included in many HIV treatment regimens to augment systemic exposure to other antiretroviral agents.

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